20-803

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SUMMARY/REVIEW OF NONCLINICAL STUDIES:

I. Studies Submitted to NDA 20-583

Loteprednol etabonate 0.2% (NDA 20-803) and loteprednol etabonate 0.5% (20-583) were developed under IND . With one exception, Study 96G-2460, Primary Ocular Irritation - FHSA, the nonclinical studies submitted to support NDA 20-803 are identical to those submitted to support 20-583. The Pharmacology/ Toxicology section of NDA 20-583 was reviewed by David A. Shriver, Ph.D. The sponsor referenced the Pharmacology/Toxicology section of NDA 20-583 to support this NDA. A copy of the summary for Dr. Shriver's review is attached; the complete review is archived with NDA 20-583. I reviewed the studies that are listed below to ensure that I agreed with Dr. Shriver's conclusions. I am in agreement with Dr. Shriver's conclusions.

Studies Submitted to NDA 20-583

Study Title	Volume:page
26-Week Ocular Dose Study in the Rabbit	9:1
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During my review of the genotoxicity studies, I noted deficiencies in the Ames and mouse lymphoma L5178Y tests. The Ames assay was conducted one time, and the results were negative. Negative results should be verified by a repeat assay; however, the sponsor did not repeat the Ames assay. In the case of the mouse lymphoma assay, negative results were obtained for the first assay. Although the sponsor repeated this assay to confirm the negative results, the second assay was unacceptable due to an inadequate response in the positive controls. Although the Ames and mouse lymphomas assays are deficient, the fact that negative results were obtained in both lends additional support to the sponsor's claim that loteprednol etabonate is nongenotoxic.

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II. Study Submitted to NDA 20-803

- **Study 96G-2460. Primary Ocular Irritation - FHSA.** (Volume 1.12page 12 004 to 12 025. This study was conducted in compliance with GLP at from December 13, 1996 to December 16, 1996.)

A. Methods: New Zealand White rabbits, 3/sex, received a 0.1 mL instillation of loteprednol etabonate 0.2% into the left eye; the right eye was left as the untreated control. The eyes were examined at 24, 48, and 72 hours post treatment. Fluorescein staining was used during the examination. The examination was facilitated by the use of slit lamp. The rabbits were observed daily for clinical signs. The rabbits were weighed at the end of the study.

B. Results:

1. Ocular Irritation: No macroscopic alterations to the cornea, iris, or conjunctiva were evident in the treated or control eyes at 24, 48, or 72 hours.

2. Clinical Signs: The rabbits did not exhibit any effects.

3. Body Weight: Treatment had no effect on body weight.

C. Conclusion: Loteprednol etabonate 0.2% is considered to be non-irritating to the ocular tissue of albino rabbits.

RECOMMENDATION: The recommendation for this NDA is approval.

RECOMMENDATIONS FOR LABELING:

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, three *in vitro* tests. *In vivo* evidence of genotoxicty, an increased frequency of micronucleated immature erythrocytes, was not observed in mice that received a single 4 gm/kg dose of loteprednol etabonate (20,000 times the maximum daily clinical dose based on mg/m^2). Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively, based on mg/m^2) prior to and during mating did not impair fertility in either gender.

Pregnancy: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of menigiocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day/day (60 times the maximum daily clinical dose based on mg/m^2), a dose which caused no maternal toxicity; the no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (10 times the maximum daily clinical dose based on mg/m^2).

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Oral treatment of rats during organogenesis with 50 or 100 mg/kg/day (500 and 1000 times the maximum clinical dose, respectively, based on mg/m^2) resulted in embyotoxicity (increased post-implantation losses with 100 mg/kg/day, and decreased fetal body weight and skeletal ossification with 50 and 100 mg/kg/day); doses of 5 (50 times the maximum daily clinical dose based on mg/m^2), 50 and 100 mg/kg/day caused teratogenicity (absent innominate artery at all doses, and cleft palate and umbilical hernia at 50 and 100 mg/kg/day). Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of 5 to 100 mg/kg/day but not at 0.5 mg/kg/day. The NOELs for the embryotoxic and teratogenic effects in rats were 5 mg/kg/day and 0.5 mg/kg/day (5 times the maximum daily clinical dose based on mg/m^2) for embryotoxicity and teratogenicity, respectively.

Oral exposure of pregnant rats to 5 and 50 mg/kg/day of loteprednol etabonate during the fetal period, a maternally toxic treatment regimen (significantly decreased body weight gain), resulted in teratogenicity (umbilical herniation) and embryotoxicity (decreased fetal birth weight); the NOEL for these effects was 0.5 mg/kg/day. Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5.0 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg day during the fetal period.

Oral treatment of female rats with 25 mg/kg/day (250 times the maximum daily clinical dose based on mg/m^2) from prior to mating through parturition increased the duration of gestation.

[Reviewer's Comment: *The maximum clinical daily dose and the dose multiples were calculated as shown below:*

Clinical dose

0.2% = 0.2 gm/100 mL = 0.002 mg/uL
Assuming a 50 uL drop will be instilled into each eye 4 times daily the following calculation was made: 0.002 mg/uL x 50 uL/drop x 8 drops/day = 0.8 mg/day
Assuming a body weight of 50 kg, the dose will be 0.8 mg/day/50 kg = 0.016 mg/kg/day

Dose multiples

The calculation for the dose multiples are presented in the table below. The animal doses are those that were used in the labeling; the human dose is the maximum daily clinical dose.

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Dose Multiples for NDA 20-803

Species	Dose in mg/kg/day	km	Dose in mg/m^2 (mg/kg x km)	Dose multiples (Nonclinical dose/clinical dose)
Mouse	4000	3	12,000	20,000
Rabbit	3	12	36	60
	0.5		6	10
Rat	0.5	6	3	5
	5		30	50
	25		150	250
	50		300	500
	100		600	1000
Human	0.016	37	0.60	—

4-21-97

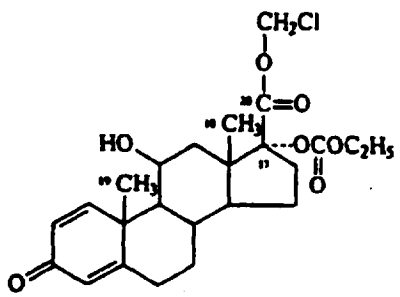
Andrea B. Weir, Ph.D.
Reviewing Pharmacologist

cc:
Original NDA 20-803
HFD-550/Division Files
HFD-550/PM/Gunter
HFD-550/PM/Holmes
HFD-550/MO/Chambers
HFD-550/Pharm TL/Chen Conrad N. Chen 4-24-97
HFD-550/Pharm/Weir

Review and Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products (HFD-540)

NDA#:	20-583 (Original and Amendments 002, 003 & 004)
Date Submitted:	3/29/95
Date CDER Received:	3/31/95
Date Assigned:	4/5/95
Date First Draft:	8/13/95
Date Review Completed:	10/16/95
Date Accepted by Supervisor:	10/16/95
Sponsor:	Pharmos Corp.
Authorized Representative:	John F. Howes, Ph.D. Vice President Clinical and Regulatory Affairs Pharmos Corp. 2 Innovation Dr. Alachua, FL 32615 Phone: (904) 462-1210 Fax: (904) 462-5236
Name of Drug:	Lotemax®; loteprednol etabonate (LE); Chloromethyl-17α-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-diene-3-one-17β carboxylate, P-5604, OPC-5604

Structure:



Loteprednol etabonate (P-5604)

Formula Weight:	466.96
Empirical Formula:	$C_{24}H_{31}O_7Cl$

Solubility:

Solvent	% Solubility
DMF	34 (340 mg/ml)
DMSO	31 (310 mg/ml)
EtOH	0.836 (8.36 mg/ml)
PEG	0.22 (2.2 mg/ml)
Water	0.0008 (8μg/ml)

Pharmacological Category: A glucocorticoid corticosteroid with no detectable mineralocorticoid activity

Related Submissions:

Review Objectives: Review the preclinical animal safety data for LE to evaluate and characterize the local and systemic toxicity of LE, and determine if the proposed labeling adequately describes the potential risks associated with use of this compound.

Background: Anti-inflammatory therapy for the eye is an important pharmacologic tool for treatment of inflammation. While potent and effective agents exist they are not without significant side effect potential; therefore, they are most often administered topically to the eye and even this localization does not eliminate untoward systemic and ocular effect of these drugs. Loteprednol was synthesized i.e., a compound that would be intrinsically active at the site of administration, but be rapidly metabolized to an inactive compound following absorption. The hoped for advantage is that they exert their effect locally and are inactivated before they are exposed to other organs.

Prednisolone

Expected toxicology of class: The ocular complications associated with corticosteroid use include posterior subcapsular cataract formation, elevation of intraocular pressure (IOP) and resultant steroid-induce glaucoma, secondary ocular infection, delayed wound healing, uveitis, mydriasis, transient ocular discomfort, and ptosis. Additionally, topical ophthalmic steroids may cause systemic effects such as adrenal insufficiency, osteoporosis, hypertension, muscular weakness or atrophy, Cushing's Syndrome, peptic ulcers inhibition of growth, diabetes, and mood changes.

Ocular adverse of adrenocorticosteroid include glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary to ocular infection form pathogens including herpes simplex, perforation of the globe.

Systemic adverse effects of adrenocorticosteroid can occur as a result withdrawal or from continual use. In humans the withdrawal syndrome consists of fever, myalgia, arthralgia, and malaise.

The use of corticosteroids for days or a few weeks does not lead to adrenal insufficiency upon cessation of treatment, but prolonged therapy may result in suppression of pituitary-adrenal function that may be slow in returning to normal.

In addition to obtunding the pituitary-adrenal axis, the principal complications resulting from prolonged therapy are fluid and electrolyte disturbances; hypertension; hyperglycemia; and glucosuria; increased susceptibility to infections; peptic ulcer; osteoporosis; a characteristic myopathy; behavioral disturbances; arrested growth and Cushing's habitus, consisting of "moon face," "buffalo hump," enlargement of supraclavicular fat pads, "central obesity," striae, ecchymoses, acne and hirsutism.

Indication: Treatment of inflammatory conditions of the anterior segment of the eye.
Treatment of allergic conditions of the conjunctiva and cornea.

Route of Administration: Topically to the eye

Dose: One to two drops of 0.5% suspension qid. During the initial 24 to 48 hours the dosage may be safely increased to two drops every two hours.

Formulation:

Ingredient	%
Loteprednol etabonate	
Povidone , USP	
Benzalkonium Chloride	
Glycerin, USP	
Tyloxapol, USP*	
Purified Water, USP	QS to 100%

* 2-(2-Isopropyl-5-methylphenoxymethlyl)-2-imidazoline - surfactant, detergent

Preclinical Efficacy Studies:

The preclinical animal efficacy data are not being reviewed for the NDA because they were previously reviewed
and also efficacy will be measured by the clinical studies.

Review perspective:

are compounds synthesized so that when administered locally, have their therapeutic effect, but when absorbed they are rapidly metabolized to an inactive moiety. In this way the body burden of a potent and active compound is substantially reduced. So the expectation for LE is that local application to the eye would achieve a local anti-inflammatory effect without achieving significant plasma levels.

In normal human subjects given eye drops 8 times-a-day for two days and then 4 times-a-day for 41 days, for detecting LE and PJ-91 showed that all samples collected over a two hour period following the 1st and 5th doses on Day 0 and then once on Days 7, 14, 21, 28, 35 and 42 (samples collected over a two hour period following dose 4) were below the limits of quantitation. These data confirm that LE that behaves as a (ref. NDA 20-583, 1:166).

In a pilot study using method[2] oral administration of 40 mg of LE resulted in detection of both in human plasma. Levels were and no pharmacokinetic parameters could be calculated.

Since this compound is intended to be administered by the topical route to the eye it is important to estimate the maximum potential daily dose that could be absorbed if all the administered drug substance were totally absorbed. The maximum human dose is 2 drops Q2H during the initial 24 to 48 hours. This makes the total maximum exposure for the first two days of therapy a maximum possible of 6 mg (5 mg/ml x 0.05 ml/drop x 2 drop/dose x 12 dose/day) and for the duration of the therapy the dose will be a maximum of 2 mg. If these doses are converted to mg/m^2 the for a 60 kg ($1.6m^2$) patient the maximum possible dose could be 33 $\mu g/kg$ or 1.25 mg/m^2. If the body surface for a 150 g rat is 0.025 m^2 and for a 1.5 kg rabbit is 0.127 m^2 then the doses in mg/ m^2 are:

Dose (mg/kg)	Dose (mg/m^2)			
	Rat	Rat	Rabbit	Human
	0.150kg	0.200kg	1.5kg	60kg
	0.025 m^2	0.035 m^2	0.127 m^2	1.6 m^2
0.1*	0.6	0.89	1.2	3.8
0.5	3	2.8	5.9	18.8
3	18	17.1	35.4	112.5
5	30	28.6	59	188
50	300	285	590	1875
100	600	571	1181	3750

* The maximum human dose (6 mg divided by 60 kg)

Animal Safety Studies:

The following studies have been performed in support of this NDA:

Animal Safety Studies:

Study Title	Species	Route	Study Duration (Day)	Study Number (GLP)	Vol:pg	Study Site
P-5604 Acute Oral Toxicity in the Mouse	Mouse	p.o.	1	PTC/2 (yes)	6:33	1
P-5604 - Acute Oral Toxicity in the Rat	Rat	p.o.	1	PTC/1/88 (yes)	6:2	1
Acute Subcutaneous Toxicity in the Mouse	Mouse	s.c.	1	PTC/4 (yes)	6:154	1
Acute Subcutaneous Toxicity in the Rat	Rat	s.c.	1	PTC/3/88 (yes)	6:115	1
P-5604 Eye Irritation Study 0.1%	Rabbit	Ocular	1	PTC/5/A (yes)	6:205	1

P-5604 Eye Irritation Study 0.5%	Rabbit	Ocular	1	PTC/57 (yes)	6:219	1
P-5604 - 7 Day Ocular Dose Range finding Study in the Rabbit	Rabbit	Ocular	7	PTC/6 (yes)	7:185	1
28 Day Ocular Range finding Study in the Rabbit	Rabbit	Ocular	28	PTC/7/88 (yes)	7:228	1
P-5604 - 28 Day Oral (Gavage) toxicity study in the Rat	Rat	p.o.	28	PTC/9 (yes)	7:1	1
26 -Week Ocular Dose Study in the Rabbit	Rabbit	Ocular	182	PTC/89/94 (yes)	9:1	1
52 Week Ocular Toxicity Study in the Dog	Dog	Ocular	367	PTC/74/91 (yes)	8:1	1

Reproductive Studies:

Study Title	Species (Strain)	Route	Study Number (GLP)	Vol:pg	Study Site
P-5604 . Rat general reproductive performance dose ranging study	Rat	p.o.	PTC/48/89 (yes)	12:339	1
Fertility and General Reproductive Study	Rat	p.o.	PTC/50 (yes)	13:155	1
P-5604 Rat Teratology Study	Rat	p.o.	PTC/49/89 (yes)	13:1	1
P-5604 Peri and Post Natal Study	Rat (Crl:CD-1(ICR)BR)	p.o.	PTC/51 (yes)	14:1	1
Rabbit Teratology Range Finding Study	Rabbit	p.o.	PTC/46/89 (yes)	12:113	1
Loteprednol Etabonate Rabbit Teratology Study	Rabbit	p.o.	PTC/67/90 (yes)	12:208	1

Pharmacokinetic Studies:

Study Title	Species	Route	Study Duration (Day)	Study Number (GLP)	Vol:pg	Study Site
Pharmacokinetics, Metabolism and Excretion of a Soft Corticosteroid, Loteprednol Etabonate	Rat	i.v.	1	PHA-34 (yes)	15:176	2
Pharmacokinetics of Loteprednol Etabonate in Dogs	Dog	i.v. & p.o.	1	PHA-27 (yes)	15:94	2
Protein binding, erythrocyte partition and stability of the steroidal anti-inflammatory drug loteprednol etabonate in dog blood and plasma - Part 1 Stability of Loteprednol Etabonate in Dog Blood and Plasma	Dog	In Vitro	1	PHA-27A (no)	15:223	2
Protein binding, erythrocyte partition and stability of the steroidal anti-inflammatory drug loteprednol etabonate in dog blood and plasma Part 2 Protein binding and Erythrocyte Partition	Dog	In Vitro	1	PHA-27B (no)	15:241	2
Hydrolysis of loteprednol etabonate in plasma samples from rats, rabbits, beagles and humans and human liver In Vitro	Rat, Dog, Rabbit, Human	In Vitro	1	PHA-5A (yes)	15:209	3
Preliminary evaluation of Oral Absorption and Distribution of the Steroidal anti-inflammatory drug Loteprednol Etabonate in Rabbits	Rabbit	Ocular	1	PHA-25 (yes)	15:1	2
Preliminary Evaluation of Oral Absorption and Distribution of the Steroidal Anti-inflammatory Drug Loteprednol Etabonate in Rats	Rat	p.o.	1	PHA-26 (yes)	15:47	2

Genotoxicity Studies:

Study Title	Species	Route	Study Number (GLP)	Vol:pg	Study Site
Mutagenicity Study of OPC-5604 by the Ames Test and in E. coli	E. coli, WP2uvrA; S. typhimurium TA 1535, TA1537, TA1538, TA100 & TA98	In Vitro	PTC/1431 (yes)	14:153	3
Metaphase Analysis of human lymphocytes treated with P-5604	Human	In Vitro	PTC/10/M (yes)	14:132	1

Mouse lymphoma L5178Y	Mouse	In Vitro	PTC 24596 (yes)	14:210	1
Mutagenicity Study of OPC-5604 by the	S. typhimurium	In Vitro	PTC/1430 (yes)	14:116	3
Mouse Micronucleus Test	Mouse	In Vivo	PTC 24595 (yes)	14:178	1

Studies with PJ-90-(Secondary Metabolite):

Study Title	Species	Route	Study Duration (Day)	Study Number (GLP)	Vol:pg	Study Site
PJ-90 Primary Eye Irritation Test in the Rabbit	Rabbit	Ocular	1	A/E40367 (yes)	6:257	1
PJ-90 Acute Subcutaneous Toxicity in the Rat	Rat	s.c.	1	A/MISC/40368 (yes)	6:190	1
PJ-90 (0.5%) 28 Day Ocular Tolerance Study in Rabbits	Rabbit	Ocular	28	PTC/92/A (yes)	12:53	1

The above studies were conducted at the following study sites:

Number	Study Site
1	
2	
3	

Animal Safety Studies:

Acute and Subchronic Studies:

The presentation of the information conveyed in this review of NDA 20-583 will be presented as summaries and details of the individual studies will be appended at the end followed by copies of the previous reviews.

LE has been evaluated for toxicity in mice and rat following single dose (table 1) and 4 week (table 2) parental administration.

Table 1 Effects of Single Systemic Dose Administration of LE or PJ-90 on 14 day Survival in Rats and Mice

Compound	Species	Route	Maximally Tolerated Dose	Study Number (Vol.:Pg.)
Loteprednol etabonate	Rat	p.o.	>4 g/kg	PTC/1/88 (6:2)
		s.c.	>1.3 g/kg	PTC/3/88 (6:115)
	Mouse	p.o.	4 g/kg	PTC/2 (6:33)
		s.c.	>1.3 g/kg	PTC/4 (6:154)
Secondary Metabolite (PJ-90)*	Rat	s.c.	>100 mg/kg	A/MISC/40358 (6:190)

* see metabolic scheme above

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Table 2 Effects of Multiple Systemic Doses of LE Administration in Rats

Species	Route	Study Duration	Comments	Study Number (Vol.:Pg.)
Rat	Oral	28 Days	A daily dose of 0.5, 5.0 & 50 mg/kg of LE caused a dose dependent reduction in body weight gain (9 and 10% for males and females, respectively for high dose rats) decreases (approx. 19 and 33% for spleen and thymus, respectively) in organ to body weight ratios and histological and blood count changes that are consistent with immune suppression. Oral administration of daily doses of 5.0 and 50 mg/kg has adverse effects in rats.	PTC/9/88 (7:1)

Ocular Administration:

Effects of ocular administration to rabbits and dogs are presented in tables 3 and 4.

Table 3 Effects of Ocular Administration of LE or PJ-90 to Rabbits

Compound [Study Number (Vol.:Pg.)	Study Duration	Vehicle	Maximally Tolerated Dose
LE [PTC/5/A (6:209) & PTC/57/A (6:219)]	Single	20% HPCD*	Single daily dose 0.1 ml of 0.1 or 0.5% suspension caused slight conjunctival redness at 1 hr after administration
[PTC/6/88 7:185]	7 days	50% HPCD	Daily doses of 0.1 ml of 0.5, 0.7 or 5.0%w/v suspensions caused a decrease in the organ weights of the thymus, adrenals and gonads.

[PTC/7/88 (7:228)]	28 days	50% HPCD	Test article was administered once-a-day. Concentrations of active in 0.1 and 0.7% formulations could not be reliably delivered, but the 5.0% formulation was within 10% of expected concentration for the last 3 weeks of the experiment. The decreased thymus, adrenal and gonad weights observed in the 7 day range finding study were not repeated and the results suggest that administration of a concentration that was 10 times the clinical concentration was well tolerated.
[PTC/89/94 (9:1)]	26 weeks	Clinical Formulation	Intraocular administration of one drop (~30μl) of a 0.5% suspension qid caused no biologically meaningful differences in the rate of body weight gain or food consumption. There were some differences in the ratio of organ weight to body weight (namely decreased adrenals, lungs (males) and ovaries); but adverse histologic effects did not accompany these weight changes. A low incidence of slight conjunctival erythema was seen at 13 weeks, but was not observed at 26 weeks and often a clear watery conjunctival discharge was noted in about half the rabbits in the treated group (no data is presented for the vehicle treated control treated rabbits). In two treated males this discharge was noted as bilateral.
Secondary Metabolite (PJ-90) [A/E 4036 (6:257)]	Single	Not specified	Formulation is not specified. After administration of 0.1 ml of a 0.1% suspension slight conjunctival redness was observed after 1 hr which resolved by 24 hrs.
[PTC/92/A (12:92)]	28 days	50% HPCD	Macroscopic and histologic examination of 0.5% PJ-90 treated rabbit eyes showed no differences from the contralateral vehicle treated eyes, however, no data were provided to support that the formulation could reliably deliver the specified dose of test compound.

* 2-hydroxypropyl-β-cyclodextrin (HPCD)

Table 4 Effects of Multiple Ocular Doses of LE Administration in Dogs

Study Duration [Study Number (Vol.:Pg.)]	Comments
52 weeks [PTC/74/91 (8:1)]	Ocular administration of 0.05, 0.1, and 0.5% w/v suspensions of LE* to beagle dogs for 52 weeks caused a dose and time-dependent increase incidence of stromal deposits in the corneas of both genders. Elevation of IOP was also observed following loteprednol administration at 52 weeks for all doses evaluated, however, no clear dose dependency was established.
	The positive control, 0.1% dexamethasone, caused both an increase in cornea stromal deposits and IOP which increased over time. Dexamethasone also caused other signs of glucocorticoid toxicity, such as reduction in body weight gain, involution of the thymus, and decreased adrenal weights and microscopic changes typical of corticosteroids.

* Preservative: 0.01% benzalkonium chloride
Inactive: gelatin, hydroxypropyl methylcellulose, tetronic 1107, boric acid, sodium borate, edetate disodium, sodium chloride, purified water

Reproductive Review: (Study Numbers - PTC/46/89, PTC/48/89, PTC/49/89, PTC/50/90, PTC/51/90 and PTC/67/90):

Segment I:

Treatment in rats with 5.0 mg/kg (intermediate) and 25 mg/kg (high) for females and 50 mg/kg (high) for males had adverse effects in F0 males and females and F1 offspring. These adverse effects include decreased body weight gain for males and females in the F0 generation and lower fetus and pup body weight. The F1 generation failed to regain the lost body weight but were able to mate and produce offspring without any adverse effect. In these latter animals retardation or absence of ossification was noted and for the highest dose group umbical hernias were noted. Even at the low dose, 0.5 mg/kg, there was a nonstatistically different decrease in fetal and pup body weight and this continued throughout the period of observation. No adverse effects were observed in the F2 generation.

In a preliminary study parturition was delayed at the high dose.

Segment II:

In a rat teratology study oral administration of 50 and 100 mg/kg per day adversely affected both maternal and fetal weight and caused fetal toxicities. Doses of 0.5 and 5.0 mg/kg per day cause retarded ossification in the fetuses while having no deleterious effects on weight gain in the dams.

In this experiment the suspensions at the lower concentrations were not within 10% of expected, and it was difficult to predict accurately the dose administered on any one day.

In a preliminary dose-range finding rabbit teratology study, oral administration of a suspension of LE to female rabbits was toxic to both the does and their fetuses. Because of the inability to formulate reliable concentrations of LE suspensions for doses of 1.5 mg/kg and lower this study shows that doses of 3.0 mg/kg administered orally from day 6 to day 18 of pregnancy are fetotoxic. These results were not seen when the study was repeated.

Segment III:

Maternal treatment with orally administered LE during late pregnancy and lactation caused a dose dependent decrease in body weight gain with only slight decreases observed at 0.5 mg/kg and marked effects on body weight, food consumption and clinical condition at 50 mg/kg. In spite of these dramatic effects there were no effects on the onset or progress of parturition.

In the offspring, LE treatment elicited toxic changes at both 5.0 and 50 mg/kg treatments. In comparison to control pups, the high dose pups exhibited body weight and developmental retardation, poor survival, diminished clinical condition and the occurrence of umbical hernia. At the 5.0 mg/kg dose adverse effects were limited to retarded body weight at birth only and the observance of an umbical hernia in one litter.

No adverse effects were observed for either the dams or the pups in the 0.5 mg/kg dose group.

Pharmacokinetic Review (Study Numbers - PHA-25, PHA-25, PHA-26, PHA-27, PHA-27A, PHA-27B, PHA-34, PHA-35, PHA-5A and PHA-5A)

In Vitro evaluation of LE demonstrates that it is not hydrolyzed in human, dog or rabbit plasma, but is rapidly and completely hydrolyzed when incubated in rat plasma. Also incubation with human liver homogenates for 20 min caused a 27% hydrolysis and the appearance of two peaks, presumably the primary (PJ-90) and secondary metabolite (PJ-91). In dog blood studies the half-life of LE in blood and plasma is 18 and 22 hr, respectively, and the erythrocyte partition coefficient is approximately 7.8 which is about 30 times greater than the PJ-91.

In Vivo studies following intravenous administration in rats and dogs (table 5) show that loteprednol was rapidly eliminated from the systemic circulation, and that no parent compound was present in bile but significant levels of both the PJ-91 and PJ-90 were present. In dogs following intravenous administration extensive conversion to PJ-91 occurred.

Table 5 Comparison of Some Pharmacokinetic Parameters in Rats and Dogs Following Intravenous Administration of 5 mg/kg

Parameter	Rat	Dog
Mean Resident Time	0.53 hr	2.0 ± 0.3 hr
Volume of Distribution	1.44 L	43.6 ± 10.1 L
Terminal $t_{½}$	0.49 hr	2.8 ± 0.3 hr

Ocularly applied ^{14}C-LE results in distribution of parent compound into the conjunctiva, cornea, iris/ciliary body, and aqueous humor, and no detectable levels in blood. The peak concentrations were achieved within the first 0.5 to 1 hr after administration and diminished to the lowest concentration by 6 to 8 hr.

Concentrations of metabolites were highest in the cornea and peak concentrations were observed at 0.5 hr after administration.

Genotoxicity:

LE has been evaluated in a number of In Vitro and In Vivo tests for it potential for genotoxicity (table 6).

Table 6 Genotoxicity Results

Study	Test species	Results	Study Number (Vol.:Pg.)
Mutagenicity Study of OPC-5604 by Ames Test and E. coli	S. typhimurium, - and - E. coli,	LE at the limit of solubility (between 10 and 50 µg/plate) did not induce gene mutations in the bacterial strains evaluated with and without activation.	PTC/1431 (14:153)

This assay not in label

Mouse Micronucleus Test -LE	Mouse/Charles River CD-1 outbred	In previous studies in mice the maximally tolerated dose of LE was determined to be 4 g/kg and this dose had no effect on the induction of chromosomal or spindle damage in developing erythrocytes in bone marrow.	PTC 24595 (14:178)
Mutation in L5178Y Mouse Lymphoma Cells	Mouse/L5178Y lymphoma cells	In this system loteprednol was not found to induce a point mutations at the TK locus of L5178Y TK +/- cells with or without metabolic activation.	PTC 24596
Metaphase Analysis of Human Lymphocytes Treated with P-5604 (LE)	human lymphocytes	In the presence and absence of rat liver microsomal faction concentrations of 6.25, 12.5, 25 and 50μg/ml. of LE caused no statistically significant increases in chromosome aberration in human lymphocytes.*	PTC/10/M (14:132)

* It should be noted that by inspection the data appear to shows no differences from control; the statistical analysis does not appear to be appropriate for the comparisons that the sponsor has made.

Pharmacokinetic Review (Study Numbers - PHA-25, PHA-25, PHA-26, PHA-27, PHA-27A, PHA-27B, PHA-34, PHA-35, PHA-5A and PHA-5A)

In Vitro evaluation of LE demonstrates that it is not hydrolyzed in human, dog or rabbit plasma, but is rapidly and completely hydrolyzed when incubation in rat plasma. Also incubation with human liver homogenates for 20 min caused a 27% hydrolysis and the appearance of two peaks, presumably the primary (PJ-91) and secondary metabolite (PJ-90). In dogs, pharmacokinetic studies demonstrated the half-life of LE in blood and plasma is 18 and 22 hr, respectively, and the erythrocyte partition coefficient is approximately 7.8 which is about 30 times greater than the PJ-91.

In Vivo studies following intravenous administration in rats and dogs show that LE is rapidly eliminated from the systemic circulation, and that no parent compound was present in bile but significant levels of both the PJ-91 and PJ-90 were present. In dogs following intravenous administration (table 7) extensive conversion to PJ-91 occurred.

Table 7 Comparison of Some Pharmacokinetic Parameters in Rats and Dogs Following Intravenous Administration of 5 mg/kg

Parameter	Rat	Dog
Mean Resident Time	0.53 hr	2.0 ± 0.3 hr
Volume of Distribution	1.44 L	43.6 ± 10.1 L
Terminal $t_{1/2}$,	0.49 hr	2.8 ± 0.3 hr

Ocularly applied ^{14}C-LE results in distribution of parent compound into the conjunctiva, cornea, iris/ciliary body, and aqueous humor, and no detectable levels in blood. The peak concentrations were achieved within the first 0.5 to 1 hr after administration and diminished to the lowest concentration by 6 to 8 hr.

Concentration of metabolites were highest in the cornea and peak concentration were observed at 0.5 hr after administration.

Problems of Formulation:

With few exceptions the sponsor has not ensured that the dosage forms that were prepared for subsequent dosing of animals could reliable deliver the expected amount of test substance (Table 8). In the case of formulations made with they have not provided data showing that the test material was actually released or if it was released how much and at what rate it was released. In another incidence, in the rat Fertility and General Reproductive Study, PTC/50, they prepared the dosing formulation

Most often the lower concentrations of the suspensions were the ones with significantly less than expected concentration, and because systemic administration of the compound resulted in adverse reaction typical of the corticoid steroids it can be concluded that the sponsor has dosed the animals with doses that were adequate to show that the test material does have toxicity. The problem is that it is difficult to determine the relationship.

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Table 8 The Accuracy of Formulations Used to Support NDA 20-583

Animal Safety Studies:

Vehicle	Formulation Accuracy	Study Title - Study Number (Vol:pg)	Species	Route	Study Duration (Days)
50 % HPCD[1]	Not specified	P-5604 Acute Oral Toxicity in the Mouse - PTC/2 (6:33)	Mouse	p.o.	1
50 % HPCD	Not specified	Acute Subcutaneous Toxicity in the Mouse - PTC/4 (6:154)	Mouse	s.c.	1
20 % HPCD	Not specified	P-5604 Eye Irritation Study 0.1% - PTC/5/A (6:205)	Rabbit	Ocular	1
NS[2]	Not submitted	PJ-90 Primary Eye Irritation Test in the Rabbit - A/E40367 (6:257)	Rabbit	Ocular	1
20% HPCD	Not specified	P-5604 Eye Irritation Study 0.5% - PTC/57 (6:219)	Rabbit	Ocular	1
50% HPCD	Not specified	P-5604 - Acute Oral Toxicity in the Rat - PTC/1/88 (6:2)	Rat	p.o.	1
50% HPCD	Not specified	Acute Subcutaneous Toxicity in the Rat - PTC/3/88 (6:115)	Rat	s.c.	1
50% HPCD	Not specified	PJ-90 Acute Subcutaneous Toxicity in the Rat - A/MISC/40368 (6:190)	Rat	s.c.	1
50% HPCD	Not specified	P-5604 - 7 Day Ocular Dose Range finding Study in the Rabbit - PTC/6 (7:185)	Rabbit	Ocular	7

50% HPCD	Not specified	PJ-90 (0.5%) 28 Day Ocular Tolerance Study in Rabbits - PTC/92/A (12:53)	Rabbit	Ocular	28
50% HPCD	The concentration varied between of expected, however, on one occasion it was as low as 43% of expected.	28 Day Ocular Range finding Study in the Rabbit - PTC/7/88 (7:228)	Rabbit	Ocular	28
CMC[3]	Concentration varied of expected.	P-5604 - 28 Day Oral (Gavage) toxicity study in the Rat - PTC/9/88 (7:1)	Rat	p.o.	28
Clinical[4]	Not specified	26 -Week Ocular Dose Study in the Rabbit - PTC/89/94 (9:1)	Rabbit	Ocular	182
Formula[4]	Preserved formulation	52 Week Ocular Toxicity Study in the Dog - PTC/74/91 (8:1)	Dog	Ocular	367

1 2- Hydroxypropyl-β-cyclodextrin
2 Not specified
3 carboxymethylcellulose
4 See study

Reproductive Studies:

Vehicle	Formulation Accuracy	Study Title - Study Number (Vol:pg)	Species	Route
1% CMC[1]	On one occasion the range was of Theoretical values.	P-5604 Rat general reproductive performance dose ranging study - PTC/48/89 (12:339)	Rat	p.o.
1% CMC	The concentration varied from of theoretical.	Fertility and General Reproductive Study - PTC/50 (13:155)	Rat	p.o.

1% CMC	On the first occasion the range of concentrations found as a percentage of theoretical was , and on the second occasion the range was	P-5604 Rat Teratology Study - PTC/49/89 (13:1)	Rat	p.o.
1% CMC	The formulations were tested on two occasions and found to be within of theoretical.	P-5604 Peri and Post Natal Studies PTC/51 (14:1)	Rat	p.o.
1% CMC	Can only use 3 mg/kg or higher	Rabbit Teratology Range Finding Study - PTC/46/89 (12:113)	Rabbit	p.o.
1% CMC	Within 10% of expected	Loteprednol Etabonate Rabbit Teratology Study - PTC/67/90 (12:208)	Rabbit	p.o.

1 Carboxymethylcellulose

Pharmacokinetic Studies:

Vehicle	Formulation Accuracy	Study Title - Study Number (Vol:pg)	Species	Route	Study Duration (Days)
NS[1]	Not specified	Protein binding, erythrocyte partition and stability of the steroidal anti-inflammatory drug LE in dog blood and plasma - Part 1 Stability of LE in Dog Blood and Plasma - PHA-27A (15:223)	Dog	In Vitro	1
NS	Not specified	Protein binding, erythrocyte partition and stability of the steroidal anti-inflammatory drug LE in dog blood and plasma Part 2 Protein binding and Erythrocyte Partition -PHA-27B (15:241)	Dog	In Vitro	1
PEG[2] (i.v.) & CMC[3] (p.o.)	Not specified	Pharmacokinetics of Loteprednol Etabonate in Dogs - PHA-27 (15:94)	Dog	i.v. & p.o.	1

Clinical[4]	Not specified	Preliminary evaluation of Oral Absorption and Distribution of the Steroidal anti-inflammatory drug Loteprednol Etabonate in Rabbits - PHA-25 (15:1)	Rabbit	Ocular	1
1 % CMC	Not specified	Preliminary Evaluation of Oral Absorption and Distribution of the Steroidal Anti-inflammatory Drug Loteprednol Etabonate in Rats - PHA-26 (15:47)	Rat	p.o.	1
50% HPCD[4]	Not specified	Pharmacokinetics, Metabolism and Excretion of a Soft Corticosteroid, Loteprednol Etabonate - PHA-34 (15:176)	Rat	i.v.	1
NS	Not specified	Hydrolysis of loteprednol etabonate in plasma samples from rats, rabbits, beagles and humans and human liver In Vitro - PHA-5A (15:209)	Rat, Dog, Rabbit, Human	In Vitro	1

1 Not specified
2 Polyethylene glycol
3 Carboxymethylcellulose
4 2- Hydroxypropyl-β-cyclodextrin

Genotoxicity Studies:

Vehicle	Formulation Accuracy	Study Title - Study Number (Vol:pg)	Species
DMSO[1]	Not specified	Mutagenicity Study of OPC-5604 by the Ames Test - PTC/1431 (14:153)	E. coli S. typhimurium
DMSO	Not specified	Metaphase Analysis of human lymphocytes treated with P-5604 - PTC/10/M (14:132)	Human
DMSO	Not specified	Mouse lymphoma L5178Y - PTC 24596 (14:210)	Mouse
0.5% CMC[2]	Not specified	Mouse Micronucleus Test - PTG-24595 (14:178)	Mouse
DMSO	Not specified	Mutagenicity Study of OPC-5604 - PTC/1430 (14:116)	

1 Dimethylsulfoxide
2 Carboxymethylcellulose

Studies with PJ-90 (Secondary Metabolite):

Vehicle	Formulation Accuracy	Study Title - Study Number (Vol:pg)	Species	Route	Study Duration (Days)
NS[1]	Not submitted	PJ-90 Primary Eye Irritation Test in the Rabbit - A/E40367 (6:257)	Rabbit	Ocular	1
50% HPCD	Not specified	PJ-90 Acute Subcutaneous Toxicity in the Rat - A/MISC/40368 (6:190)	Rat	s.c.	1
50% HPCD	Not specified	PJ-90 (0.5%) 28 Day Ocular Tolerance Study in Rabbits - PTC/92/A (12:53)	Rabbit	Ocular	28

1 Not specified
2 2- Hydroxypropyl-β-cyclodextrin

Summary: Lotoprednol etabonate behaves as a , i.e., it rapidly degrades following administration. Administration of ^{14}C labeled LE to the eyes of rabbits results in detectable levels conjunctiva, cornea, iris/ciliary body, and aqueous humor, but little detectable levels in blood.

Lotoprednol etabonate has not been shown to have genotoxic potential.

In rats and rabbits LE is both fetotoxic and toxic to the gravid female. Like other glucocorticoids it appears to cross the placental and has effect on the rate of weight gain in the offspring. In the rabbit, the most sensitive species, a dose of 0.5 mg/kg appears to be the highest dose tolerated without either fetotoxicity or toxicity to the female. This dose is estimated to be 4 or 5 times the maximum possible total daily dose for a patient when used as directed and if only 5% is absorbed systemically, the dose could be as much as 100 times the human exposure.

Regulatory Conclusion: One of the major problems with this study is that the sponsor did not provide adequate formulation to ensure homogeneity of test material in the dosage forms administered and therefore, lower concentrations of the suspensions were often significantly less potent than expected. They also did not demonstrate that the test material was released from within the hydroxypropyl-β-cyclodextrin formulation. However, since the blood level following

following ocular application in rabbits is negligible, the risk of potential untoward effects is minimal.

From a nonclinical stand point there is no reason not to approve this drug.

Label considerations:

Systemic administration of the compound results in adverse reaction typical of the corticoid steroids, and labeling considerations related to Pregnancy Category are adequate, however, the sponsor must rewrite the sections listed under Precautions/General and Carcinogenesis, mutagenesis, impairment of fertility to:

1. List mutagenesis under the proper heading
2. Address the effect of test material on F1 and F2 fetuses

The sponsors have done no studies to investigate the carcinogenicity and have so noted in the label and there is no need to conduct such studies.

Appendix:

I. Detailed reviews of individual studies
II. Previous reviews

David A. Shriver, Ph.D.
Pharmacologist

cc:

NDA 20-583 file
HFD-340
HFD-540
HFD-540/PHARM/SHRIVER
HFD-540/MO/CARRERAS
HFD-540-CHEM/GILMAN
HFD-540/PMS/CHAPMAN
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